Versatile Synthetic Approach for Selective Diversification of Bicyclic Aza-Diketopiperazines

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S Supporting Information

ABSTRACT: Herein, we report a convenient synthesis of unprecedented aza-diketopiperazines (aza-DKPs). The strategy is based on selective diversification of bicyclic aza-DKP scaffolds by click reaction, N-acylation, and/or N-alkylation. These scaffolds containing either azido or amino groups were obtained by a key Rh(I)-catalyzed hydroformylative cyclohydrocarbonylation reaction of allyl-substituted aza-DKP. The methodology is readily amenable to the parallel synthesis of original aza-DKPs to enlarge the chemical diversity of aza-heterocycles.
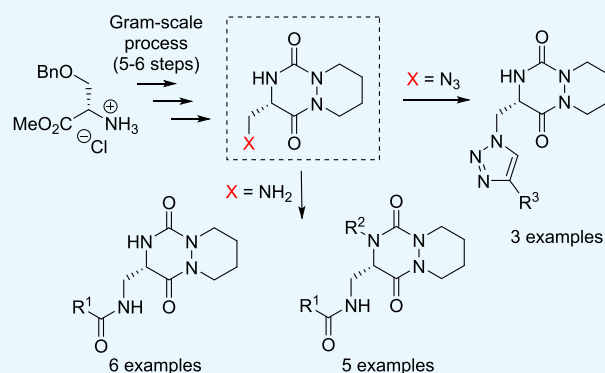
INTRODUCTION

Small heterocyclic scaffolds are of central importance in the development of novel pharmacological probes and/or drug candidates.[1] However, a recent literature analysis over the last 30 years has shown that an average of only five new ring systems per year have emerged.[2] Therefore, to enlarge the chemical diversity of scaffolds, we decided to design and to synthesize novel aza-diketopiperazines (aza-DKPs) with potential applications in medicinal chemistry. By contrast to the well-known 2,5-diketopiperazines (2,5-DKPs),[3] aza-DKPs have been much less exploited and few synthetic approaches have been reported to date.[4−10] Recently, we have shown that aza-DKPs were obtained following a deprotection/cyclization process with a higher yield than 2,5-DKPs.[10] In addition, the replacement of one Cα-stereogenic center by a nitrogen atom resulted in a significant improvement of both the water solubility and the microsomal stability of this scaffold as compared to the 2,5-DKP analogue.[10] We have also described more complex aza-DKPs readily obtained following a novel domino cyclohydrocarbonylation (CHC)/addition process.[9] This methodology enabled the rapid and efficient synthesis of novel three-dimensional (3D)-shaped bicyclic and tricyclic aza-DKP scaffolds containing sp³-hybridized carbon atoms and controlled stereocenters. Moreover, the analysis of their 3D molecular descriptors and "drug-likeness" properties highlighted not only their originality in the chemical space of aza-heterocycles but also their higher likelihood of successfully progressing through the hit-to-lead process.[9b]

Herein, we report the synthesis of novel 6,6-bicyclic aza-DKPs showing two points of diversification at N-2 and C-3 positions of the scaffold (Figure 1). Cyclic systems fused to a 2,5-DKP showed interesting biological activities.[11−13] The ability to place the different substituents in a structurally rigid three-dimensional arrangement should allow for increased selectivity toward biological targets. The N-2 and C-3 positions were selected as diversification points, as they are strategic sites of functionalization for 2,5-DKPs. For instance, the N-2 position has been used as an anchor for the design of conjugated molecules between integrin ligands and paclitaxel for the synthesis of antitumor agents.[14] In some 2,5-DKPs-based compounds such as chaetocin A[15] or E- and N-cadherin inhibitors,[16] the C-3 position is functionalized by an amido or alcohol groups. Therefore, in the strategy described herein, we have studied the possibility to introduce in this position both hydroxy- or amino-methyl groups as a starting point for the elongation of an O-alkyl or peptidic chains. The aminomethyl moiety was readily obtained from an azide derivative, which also allowed the formation of triazole rings. The latter are appealing in medicinal chemistry because they have been described as mimics of transoid amide bond which, like the aza-DKP backbone, allows to increase the metabolic stability of the synthetized molecules while maintaining biological features.[17]
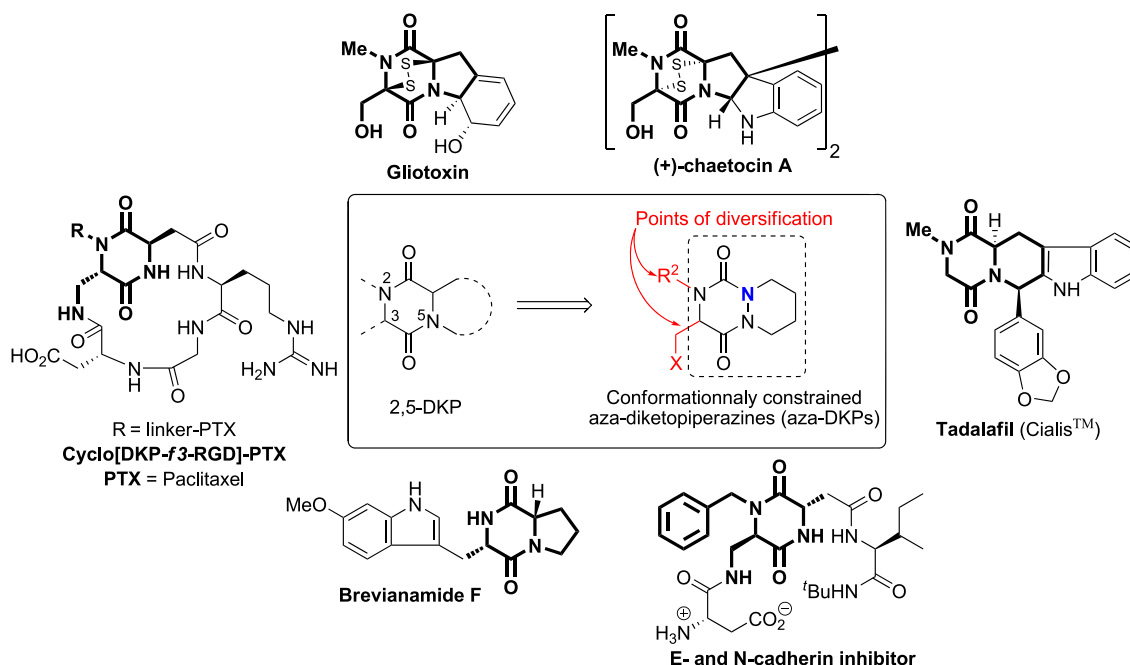
Figure 1. General structure of novel bicyclic aza-DKPs and selected examples of known biologically active 2,5-DKPs.

Thereby, we herein report an unprecedented strategy for selective diversification of aza-DKPs to rapidly access mono- or disubstituted aza-DKPs. The strategy relies on the preparation of two aza-DKP bicyclic scaffolds encompassing at C-3 position either a hydroxymethyl (**5**) or an azidomethyl (**8**) moiety (Figure 2). Thereafter, subsequent functionalization of

second point of diversification, the alkylation at N-2 was also investigated, leading to novel difunctionalized aza-DKPs. We anticipate that the strategy described herein will be useful to facilitate the parallel synthesis of complex aza-DKPs to enrich the chemical diversity of the existing chemical libraries.

Figure 2. Design of aza-DKP scaffolds **5** and **8** ready to functionalize.

these two scaffolds was evaluated and allowed access to N-acyl-, triazole-, or amido-substituted aza-DKPs. To introduce a

RESULTS AND DISCUSSION

To access scaffolds **5** and **8** displaying two sites of potential derivatization, we envisioned a straightforward synthetic approach starting from N-protected-O-benzyl-L-serine methyl ester (Figure 2). The key step of the process is based on the preparation of the allyl-substituted aza-DKP precursor[8] enabling the straightforward synthesis of the desired bicyclic aza-DKP scaffolds by cyclohydrocarbonylation reaction.[9]

Bicyclic Alcohol Functionalized Aza-DKP 5. To readily access this scaffold, the α-amino group of the commercially available O-benzyl-L-serine methyl ester was protected with the acid-sensitive p-methoxybenzyl (PMB) protecting group
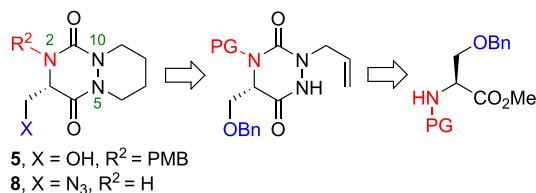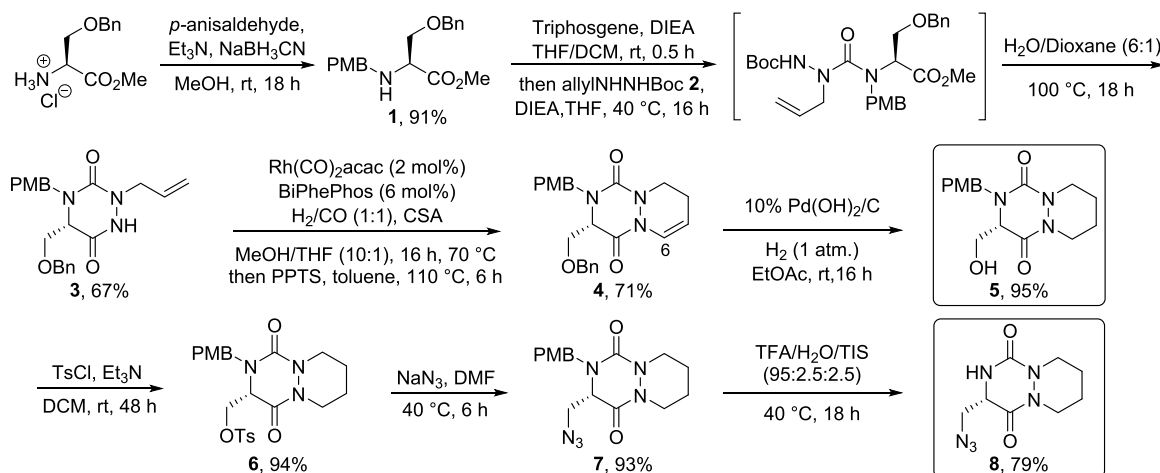
Scheme 1. Preparation of Aza-DKP Scaffolds 5 and 8

through a reductive amination in the presence of *p*-methoxybenzaldehyde leading to alkylated amino ester **1** in 91% yield (Scheme 1). The latter was then reacted with bis(trichloromethyl)-carbonate and allyl *t*-butyl carbazate **2**, obtained in one step from commercially available *t*-butyl carbazate, to provide semicarbazide intermediate. The subsequent N-Boc deprotection and cyclization were then attempted by treating crude semicarbazide with trifluoroacetic acid (TFA)/H$_2$O (95:5). Unfortunately, in these conditions, only the products arising from the simultaneous N-Boc and N-PMB deprotections were observed without ulterior cyclization. This result is consistent with our previous findings that demonstrated the necessity of starting from N-alkylated linear semicarbazide to initiate the cyclization toward aza-DKP.[8] Similar result was obtained in diluted acidic conditions (5% of TFA in dichloromethane (DCM)), attesting the highly acid-sensitive character of the PMB-protecting group. To circumvent this issue, a boiling-water-catalyzed neutral N-Boc cleavage method was applied.[18] The crude semicarbazide was dissolved in a mixture H$_2$O/1,4-dioxane (6:1) and heated to reflux for 18 h. Under these conditions, N-Boc group was removed selectively and the cyclization occurred spontaneously to provide aza-DKP **3** in 67% overall yield (two steps from **1**).

The allyl derivative **3** was then submitted to a Rh(I)-catalyzed cyclohydrocarbonylation (CHC) process to readily access bicyclic aza-DKP **4**. As previously reported, the CHC was performed under classical conditions, i.e., the use of syngas (H$_2$/CO) in the presence of Rh(I) catalyst, BiPhePhos, and CSA in tetrahydrofuran (THF).[9] However, in these conditions, a mixture of the desired bicyclic derivative **4** and the hydroxylated intermediate at C-6 position were obtained. Then, to facilitate the purification and to increase the yield of the reaction, the subsequent conversion of the hydroxyl derivative into aza-DKP **4** was attempted. However, regardless of the time, the temperature or the nature of the acid (CSA or PPTS), the full conversion of alcohol intermediate into aza-DKP **4** was never observed. To circumvent this limitation, we then envisaged a two-step process that involved the methoxylated derivative at the C-6 position and its subsequent elimination under acidic condition to provide the desired enamide **4**. Therefore, the Rh(I)-catalyzed cyclohydrocarbonylation of aza-DKP **3** was achieved in MeOH/THF (10:1), leading to the methoxylated derivative at the C-6 position, which was directly subjected to acidic conditions (PPTS) to give exclusively the enamide **4** in 71% yield. Finally, the simultaneous reduction of the alkene and the removal of the benzyl-protecting group were performed by catalytic hydrogenolysis of **4** in the presence of Pearlman's catalyst. Thereby, scaffold **5** was obtained in excellent yield (95%), ready to be further functionalized.

Bicyclic Azido Functionalized Aza-DKP 8. To design original aza-DKPs via both click chemistry and reduction/N-acylation sequence from an azido derivative, aza-DKP scaffold **8** was efficiently obtained in a three-step process starting from bicyclic compound **5** (Scheme 1). The primary alcohol was first converted into the tosylate **6** followed by nucleophilic substitution in the presence of NaN$_3$ providing azido **7** in excellent yield (93%). The PMB group was then easily removed from **7** by heating at 40 °C in TFA/H$_2$O/TIS (95:2.5:2.5) to give the deprotected aza-DKP **8** in good yield (79%), ready to react via a copper-catalyzed azide−alkyne cycloaddition.

The efficient and robust process herein developed led to the synthesis of both scaffolds **5** and **8** in 41% overall yield (five steps) and 28% overall yield (eight steps), respectively. Noteworthy, this process was readily amenable to gram-scale production of both platforms for their subsequent functionalization.

Attempts To Functionalize Aza-DKP Scaffold 5. We then turned our attention to the diversification of both scaffolds **5** and **8**. First, we examined the reactivity of primary alcohol **5** toward classical O-alkylation conditions (Scheme 2).

Scheme 2. Synthesis of Dehydroalanine-Containing Aza-DKP 9 from Aza-DKP 5 and 6
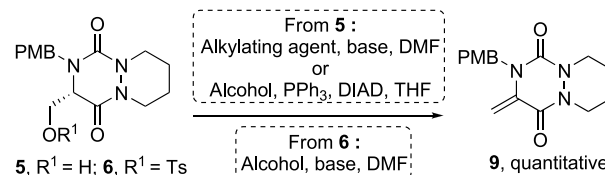
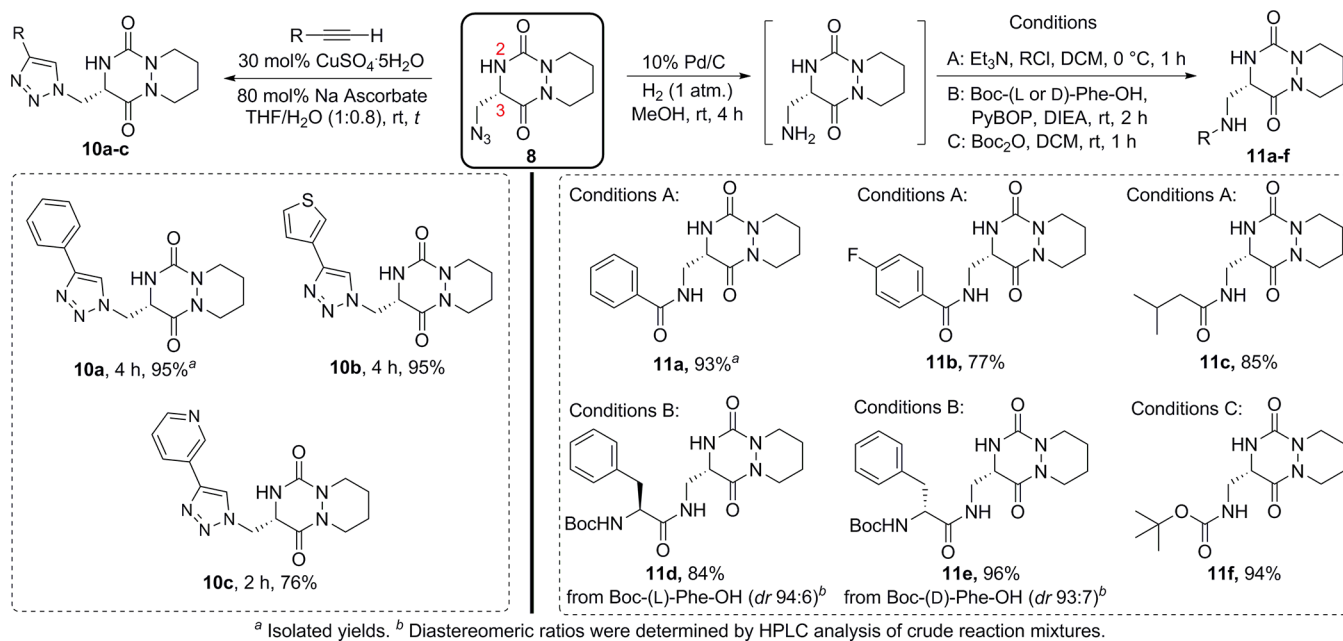The use of NaH or inorganic bases (K$_2$CO$_3$, Cs$_2$CO$_3$) in the presence of alkylating agent (allyl bromide or iodomethyl-cyclopentane) failed to provide the desired alkylated analogues. Regardless of the tested conditions, only the dehydration reaction was observed, leading to alkene **9** quasi-quantitatively.[19] To avoid dehydration reaction, the alkylation of **5** was tested under base-free conditions by employing silver salts (Ag$_2$O) and alkyl halide in DCM.[20] However, alcohol **5** proved to be unreactive toward these conditions (results not shown).

The alkylation was then envisaged following a Mitsunobu reaction. Compound **5** was reacted with PPh$_3$ and DIAD in the presence of 4-fluorophenol in THF. Unfortunately, as observed above, alkene **9** was quantitatively obtained. Finally, we tried an alternative strategy through tosylate derivative **6**, obtained during the synthesis of scaffold **8**. However, the reaction of 4-methoxyl phenol in the presence of NaH or Cs$_2$CO$_3$ in dimethylformamide (DMF) led exclusively to the dehydroalanine derivative **9**. Taken together, these results demonstrate that the O-alkylation of serine system in the presence of a strong base or via alcohol activation remains difficult due to the high propensity of the α-proton (H-3) to undergo elimination. However, it is noteworthy that dehydroalanine-containing aza-DKP **9** could be a useful substrate for further functionalization including Michael addition as well as chemoselective ligation.[21]

Derivatization of Aza-DKP Scaffold 8 via Click Chemistry. Owing to the difficulty to functionalize platform **5**, we then focused our attention on the derivatization of aza-DKP scaffold **8** under copper(I)-catalyzed azide−alkyne cycloaddition conditions (CuAAC) to introduce a triazole moiety as a bioisostere of the amide bond (Scheme 3).[17] Treatment of azido **8** with CuSO$_4$, sodium ascorbate, and phenylacetylene in THF/H$_2$O (1:0.8) at 25 °C for 4 h led to triazole-substituted aza-DKP **10a** in excellent yield (95%). This reaction was also successfully applied to other terminal alkynes substituted by heteroaryl group including thiophene and pyridine providing triazoles **10b** and **10c** in 95 and 76% yields, respectively.

Derivatization of Aza-DKP Scaffold 8 via Reduction and Subsequent N-Acylation. Taking advantage of the azido moiety, a first functionalization was envisaged following a two-step reduction/acylation process (Scheme 3). Therefore, azide **8** was submitted to catalytic hydrogenation in the
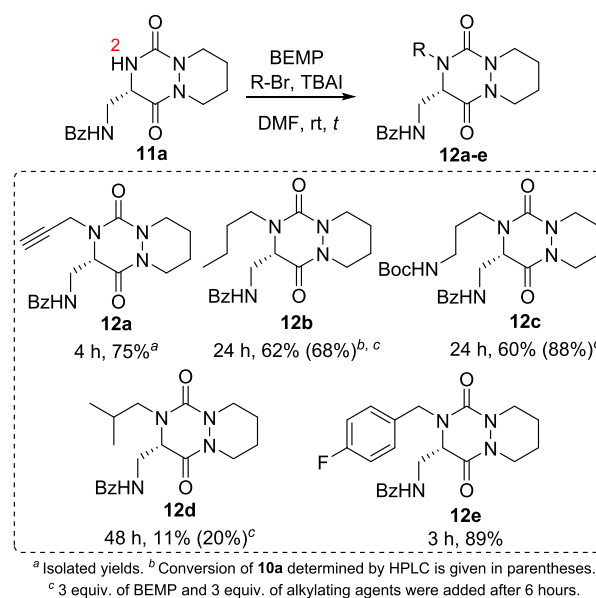
Scheme 3. Functionalization of Aza-DKP Scaffold 8

a Isolated yields. *b* Diastereomeric ratios were determined by HPLC analysis of crude reaction mixtures.

presence of H_2/Pd in MeOH to provide amine intermediate quantitatively, which was straight way engaged in the N-acylation step after a simple filtration to remove the catalyst. Thereby, the primary amine was easily coupled with acyl chloride bearing aromatic and aliphatic groups affording amides **11a−c** with yields ranging from 77 to 93%. To enrich the chemical diversity around bicyclic aza-DKPs, commercially available amino acid building blocks including Boc-(L)- and Boc-(D)-phenylalanine were also introduced via acylation under classical peptidic coupling conditions to provide diastereomers **11d** and **11e** in good yields (84 and 96%, respectively). These examples supplied information on the potential epimerization at the C-3 position all along the synthesis of azido **8**, as only diastereomers **11d** and **11e** were obtained with only slight erosion of enantioselectivity (dr ratio 94:6 and 93:7, respectively). Finally, to envision the functionalization at N-2 position before the acylation of the primary amino group, the latter was efficiently protected by *tert*-butoxycarbonyl group in the presence of di-*tert*-butyl dicarbonate (**11f**, 94%).

N-Alkylation of Monofunctionalized Aza-DKP 11a. Aiming to access difunctionalized scaffolds, the reactivity of free nitrogen-containing aza-DKP (N-2) toward N-alkylation conditions was then explored starting from N-acylated compound **11a**. Various bases including K_2CO_3, Cs_2CO_3, *t*-BuOK, or BEMP were evaluated in the presence of propargyl bromide in DMF and using tetrabutylammonium iodide (TBAI). As previously reported by Luthman et al. for the N-alkylation of free nitrogen-containing 2,5-DKPs, best conditions were obtained using the sterically hindered iminophosporane base (i.e., BEMP).[22] Thereby, after 4 h at room temperature, the propargylic derivative **12a** was isolated in 75% yield (Scheme 4). To evaluate the scope and limitation of the reaction, these conditions were then applied to diverse alkylating agents (R group, Scheme 4). Compared to the more reactive propargyl bromide, the alkylation of aza-DKP **11a** with *n*-butyl bromide (**12b**) and Boc-aminopropyl bromide (**12c**) was sluggish, with only a partial conversion

Scheme 4. Access to Disubstituted Aza-DKPs by N-Alkylation of Scaffold 11a

a Isolated yields. *b* Conversion of **10a** determined by HPLC is given in parentheses. *c* 3 equiv. of BEMP and 3 equiv. of alkylating agents were added after 6 hours.

of **11a** in a nearly 1:1 ratio after 6 h at room temperature for both alkylating agents. Whereas the extension of reaction times or heating did not improve the conversion of **11a**, the addition of 3 equiv of base and alkyl bromide proved to be beneficial and led to compounds **12b** and **12c** in 62 and 60% yields, respectively. Nevertheless, the reaction performed in the presence of sterically demanding isobutyl bromide led to a lower yield after 48 h regardless of the amount of base and alkyl bromide (**12d**, 10%). This low-yield alkylation can be ascribed to the steric hindrance of isobutyl bromide along with its propensity to undergo dehydrohalogenation (−HX) in the presence of base. Finally, the 4-fluorobenzyl group was introduced efficiently under the same conditions without the need of additional base or alkylating agent providing compound **12e** in excellent yield (89%).

Overall, this methodology allows access to novel disubstituted bicyclic aza-DKPs bearing functionalities such as propargyl or amino groups able to react with various commercial building blocks to further extend the chemical diversity of this scaffold. Noteworthy, this is a rare example of alkylation of secondary amine containing aza-urea moiety.[23]

CONCLUSIONS

In this article, we described an efficient and versatile approach for selective diversification of mono- and disubstituted bicyclic aza-DKPs to enlarge the chemical diversity accessible around this scaffold. The synthetic route involved azido scaffold **8** obtained in eight steps in 28% overall yield from the commercially available O-benzyl-L-serine methyl ester. Then, we took advantage of the double reactivity of the azido moiety to access various unprecedented aza-heterocycles such as (1) triazole-containing aza-DKPs and (2) acylated aza-DKPs obtained after the reduction of the azido function and subsequent N-acylation. To prepare disubstituted scaffolds, we have evaluated the possibility to alkylate the benzoylated intermediate. The use of sterically hindered iminophosporane base allowed us to generate various disubstituted bicyclic aza-DKPs. All attempts to alkylate scaffold **5** having led to the formation of the dehydroalanine **9**, it will be interesting to evaluate the reactivity of this new compound with various nucleophiles.

EXPERIMENTAL SECTION

General Methods. Reagents were obtained from commercial sources and used without any further purification. Thin-layer chromatography was performed on silica gel 60 F_{254} plates. (Acetylacetonato)dicarbonylrhodium(I) and dry solvents were purchased from Sigma-Aldrich. BiPhePhos was prepared as reported previously.[24] All the experiments were performed under argon atmosphere except where otherwise noted. Hydroformylation was performed in a reactor from Equilabo using 1:1 H_2/CO supplied by Airgas, Inc. Flash chromatography was performed on silica gel (60 Å, particle size 40−63 μm). Purification by semipreparative HPLC was performed on RP-18 (25−40 μm, Merck) prepacked columns on a PLC 2020 apparatus from Gilson. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded, respectively, at 400, 100, and 376 MHz with a Bruker Advance 400 spectrometer. Conditions are specified for each spectrum (temperature 25 °C unless specified). Chemical shifts are reported in parts per million (ppm) relative to residual solvent and coupling constants (J) are reported in hertz (Hz). Signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), brs (broad singlet), brd (broad doublet), brq (broad quadruplet), or a combination of the above. Specific rotations were measured on a Perkin-Elmer polarimeter using a 10 cm cell with a sodium lamp at 589 nm. High-resolution mass spectra were obtained on an Agilent Technologie 6520 Accurate-Mass Q-TOF LC/MC apparatus using electrospray ionization mode and time-of-flight analyzer (ESI-TOF).

General Procedure A. To a degassed solution of **8** (1 equiv) in a mixture THF/H_2O (1:0.8, 15 mL mmol^{-1}) were successively added heteroarylacetylene (1.1 equiv), sodium ascorbate (0.8 equiv), and CuSO$_4$·5H$_2$O (0.3 equiv) at room temperature under argon. The resulting solution was degassed for 5 min and then stirred at room temperature for 4 h under argon. This mixture was then concentrated in vacuo and the

resulting residue was partitioned between EtOAc (125 mL mmol^{-1}) and saturated aqueous NH$_4$Cl solution (62.5 mL mmol^{-1}). The aqueous layer was extracted three times with EtOAc (125 mL mmol^{-1}), the combined organic layers were washed with brine (250 mL mmol^{-1}), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (gradient 50−95% of EtOAc in n-pentane).

General Procedure B. To a solution of **8** (1 equiv) in dry MeOH (11.2 mL mmol^{-1}) was added 10 wt % Pd on carbon under argon. The resulting mixture was stirred at room temperature under a hydrogen atmosphere for 3 h. The reaction mixture was filtered over a pad of Celite and washed twice with MeOH (22.4 mL mmol^{-1}). The filtrate was concentrated in vacuo and the resulting residue was used as such in the next step. To a solution of the crude mixture in dry DCM (9.0 mL mmol^{-1}) were added successively Et$_3$N (1.2 equiv) and acid chloride (1.1 equiv) dropwise at 0 °C under argon. The reaction mixture was stirred at 0 °C for 1 h under argon. The resulting mixture was diluted with DCM (44.8 mL mmol^{-1}) and H$_2$O (22.4 mL mmol^{-1}) and the aqueous layer was extracted three times with DCM (44.8 mL mmol^{-1}). The combined organic layers were washed with brine (112 mL mmol^{-1}), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (gradient 0−3% of MeOH in DCM).

General Procedure C. To a solution of **8** (1 equiv) in dry MeOH (11.2 mL mmol^{-1}) was added 10 wt % Pd on carbon under argon. The resulting mixture was stirred at room temperature under a hydrogen atmosphere for 3 h. The reaction mixture was filtered over a pad of Celite, which was washed twice with MeOH (22.4 mL mmol^{-1}). The filtrate was concentrated in vacuo and the resulting residue was used as such in the next step. To a solution of the crude mixture in dry DMF (11 mL mmol^{-1}) were added successively PyBOP (1.1 equiv), Boc-amino acid (1.1 equiv), and N,N-diisopropylethylamine (DIEA, 4 equiv) at room temperature under argon. The reaction mixture was stirred for 2 h at this temperature under argon and then concentrated in vacuo. The resulting residue was diluted with DCM (22.4 mL mmol^{-1}) and H$_2$O (11.2 mL mmol^{-1}) and the aqueous layer was extracted three times with DCM (22.4 mL mmol^{-1}). The combined organic layers were washed with brine (56 mL mmol^{-1}), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (gradient 0−3% of MeOH in DCM).

General Procedure D. To a solution of **11a** (1 equiv) in dry DMF (10.1 mL mmol^{-1}) were added successively BEMP (3 equiv), TBAI (3 equiv), and an alkylating agent (5 equiv) at room temperature under argon. The resulting mixture was stirred for 3−48 h at this temperature under argon. The resulting solution was then diluted with H$_2$O (50 mL mmol^{-1}) and extracted three times with EtOAc (150 mL mmol^{-1}). The combined organic layers were washed with brine (300 mL mmol^{-1}), dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (gradient 0−80% of EtOAc in n-pentane).

O-Benzyl-N-(4-methoxybenzyl)-L-serine Methyl Ester (1).[25] To a solution of O-benzyl-L-serine methyl ester hydrochloride (2.70 g, 10.9 mmol, 1 equiv) in anhydrous methanol (95 mL) was added triethylamine (1.53 mL, 10.9 mmol, 1 equiv) at room temperature under argon. The reaction mixture was stirred for 10 min and p-anisaldehyde (1.20 mL, 9.9 mmol, 0.9

equiv) was then added. After stirring for 1 h, the solution was cooled to 0 °C and then acetic acid (1.26 mL, 16.5 mmol, 2 equiv) and NaBH$_3$CN (1.04 g, 16.5 mmol, 1.5 equiv) were successively added. The resulting solution was stirred at 0−5 °C for 1 h and then at room temperature for a further 18 h under argon. Solid NaHCO$_3$ (2.77 g, 32.9 mmol, 3 equiv) was added and the solvent was removed under reduced pressure. The resulting white residue was partitioned between DCM (170 mL) and H$_2$O (80 mL) and the aqueous layer was extracted with DCM (2 × 170 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (0−20% of EtOAc in n-pentane) affording **1** as a colorless oil (2.95 g, 8.96 mmol, 91%). R_f = 0.28 (n-pentane/EtOAc, 3:2); $[\alpha]_D^{20}$ = −8.53 (c 0.23, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36−7.26 (m, 5H), 7.25 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.54 (d, J = 12.2 Hz, 1H), 4.49 (d, J = 12.2 Hz, 1H), 3.83 (d, J = 12.8 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.72−3.65 (m, 2H), 3.65 (d, J = 12.8 Hz, 1H), 3.51 (t, J = 4.9 Hz, 1H), 2.05 (brs, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 173.6, 158.7, 137.9, 131.7, 129.5 (2C), 128.3 (2C), 127.6, 127.6 (2C), 113.8 (2C), 73.2, 71.0, 60.4, 55.2, 51.9, 51.4; HRMS (ESI-TOF): calcd for C$_{19}$H$_{24}$NO$_4$ [M + H]$^+$ 330.1705, found 330.1704.

tert-Butyl 2-Allylhydrazinecarboxylate (**2**).[9a] To a dry 100 mL flask were added *tert*-butyl carbazate (4.22 g, 31.9 mmol, 3 equiv), potassium carbonate (1.47 g, 10.6 mmol, 1 equiv), and anhydrous THF/DMF (9:1, 30.7 mL). The suspension was heated to 80 °C. A solution of allyl bromide (920 μL, 10.6 mmol, 1 equiv) in a mixture THF/DMF (9:1, 4 mL) was added over 3 h and the mixture was stirred overnight at 80 °C. The mixture was then concentrated in vacuo to a slurry and the crude was diluted with H$_2$O/EtOAc (1:1, 400 mL). The aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (0−25% of EtOAc in n-heptane) yielding **2** (1.21 g, 7.02 mmol, 66%) as a colorless oil. R_f = 0.26 (n-heptane/EtOAc, 7:3); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.17 (brs, 1H), 5.84 (ddt, J = 16.6, 10.4, 6.3 Hz, 1H), 5.22 (brd, J = 17.1 Hz, 1H), 5.16 (brd, J = 10.2 Hz, 1H), 4.00 (brs, 1H), 3.46 (d, J = 6.3 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.7, 134.2, 118.0, 80.4, 54.6, 28.3 (3C).

(S)-2-Allyl-5-((benzyloxy)methyl)-4-(4-methoxybenzyl)-1,2,4-triazinane-3,6-dione (**3**). To a solution of triphosgene (0.315 g, 1.06 mmol, 0.35 equiv) in anhydrous THF (20 mL), under argon, was added dropwise (over 10 min) a solution of **1** (1.00 g, 3.04 mmol, 1 equiv) and DIEA (0.578 mL, 3.34 mmol, 1.1 equiv) in a mixture of anhydrous THF/DCM (2:1, 12 mL). The resulting mixture was stirred at room temperature for 25 min. A solution of **2** (0.549 g, 3.19 mmol, 1.05 equiv) and DIEA (0.578 mL, 3.34 mmol, 1.1 equiv) in anhydrous THF (6 mL) was then added dropwise and the mixture was heated at 40 °C overnight. The mixture was evaporated in vacuo, partitioned between EtOAc (150 mL) and H$_2$O (50 mL), and the aqueous layer was re-extracted twice with EtOAc (2 × 150 mL). The combined organic layers were washed successively with an aqueous solution of citric acid (5%, 100 mL), a saturated solution of NaHCO$_3$ (100 mL) and with brine (100 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. In a sealed flask, the crude residue was dissolved in 1,4-dioxane (24 mL) and H$_2$O (140 mL) was

added. The mixture was heated overnight at 120 °C and evaporated under reduced pressure. The crude residue was diluted with EtOAc/H$_2$O (2:1, 150 mL) and the aqueous layer was extracted twice with EtOAc (2 × 75 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (gradient 0− 50% of EtOAc in n-pentane) leading to **3** (0.800 g, 2.02 mmol, 67%) as a colorless oil. R_f = 0.27 (n-pentane/EtOAc, 1:1); $[\alpha]_D^{20}$ = +28.6 (c 0.20, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.74 (brs, 1H), 7.38−7.29 (m, 5H), 7.19 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 5.75 (dddd, J = 17.2, 10.2, 7.2, 5.7 Hz, 1H), 5.26−5.18 (m, 2H), 4.94 (d, J = 14.9 Hz, 1H), 4.49 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 11.8 Hz, 1H), 4.25 (dd, J = 15.3, 5.4 Hz, 1H), 4.07 (d, J = 14.9 Hz, 1H), 3.85 (t, J = 3.5 Hz, 1H), 3.83−3.78 (m, 4H), 3.66 (dd, J = 9.9, 3.4 Hz, 1H), 3.55 (dd, J = 9.9, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 164.1, 159.4, 154.2, 137.1, 131.6, 129.7 (2C), 128.5 (2C), 128.1, 128.0, 127.9 (2C), 120.2, 114.2 (2C), 73.6, 67.1, 58.9, 55.3, 52.1, 48.6; HRMS (ESI-TOF): calcd for C$_{22}$H$_{26}$N$_3$O$_4$ [M + H]$^+$ 396.1923, found 396.1912.

(S)-3-((Benzyloxy)methyl)-2-(4-methoxybenzyl)-2,3,8,9-tetrahydropyridazino[1,2-a][1,2,4]triazine-1,4-dione (**4**). In a Schlenk glassware under argon were added Rh(CO)$_2$(acac) (13 mg, 0.051 mmol, 0.02 equiv) and anhydrous THF (4 mL). BiPhePhos (0.119 g, 0.152 mmol, 0.06 equiv) was then added at room temperature and this mixture was stirred at this temperature for 10 min. The resulting solution was introduced under argon into a stainless steel autoclave containing a solution of **3** (1.00 g, 2.53 mmol, 1 equiv) and camphor sulfonic acid (0.176 g, 0.759 mmol, 0.3 equiv) in anhydrous methanol (40 mL). The reactor was purged three times with H$_2$/CO (1:1, 5 bars) and filled with H$_2$/CO (1:1, 5 bar). The reactor was heated to 70 °C and stirred for 16 h. The reactor was then cooled to room temperature and vented to atmospheric pressure. The reaction mixture was quenched with solid NaHCO$_3$ (0.425 g, 5.06 mmol, 2 equiv) and then evaporated in vacuo. The resulting residue was partitioned between EtOAc (50 mL) and H$_2$O (25 mL) and the aqueous layer was re-extracted twice with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. To a solution of the crude residue in anhydrous toluene (45 mL) was added pyridinium *p*-toluenesulfonate (0.318 g, 1.26 mmol, 0.5 equiv) at room temperature under argon. The reaction mixture was heated at 110 °C for 6 h. The resulting mixture was then cooled to room temperature, quenched with solid NaHCO$_3$ (0.425 g, 5.06 mmol, 2 equiv), and evaporated in vacuo. The resulting residue was partitioned between EtOAc (50 mL) and H$_2$O (25 mL) and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (gradient 0−25% of EtOAc in n-pentane) leading to **4** as a colorless oil (0.732 g, 1.79 mmol, 71%). R_f = 0.47 (n-pentane/EtOAc, 1:1); $[\alpha]_D^{20}$ = +118.8 (c 0.18, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37−7.27 (m, 5H), 7.20 (d, J = 8.6 Hz, 2H), 7.06 (dd, J = 8.4, 1.5 Hz, 1H), 6.84 (d, J = 8.6 Hz, 2H), 5.29 (brt, J = 6.4 Hz, 1H), 4.89 (d, J = 14.8 Hz, 1H), 4.51−4.46 (m, 1H), 4.46 (d, J = 11.6 Hz, 1H), 4.41 (d, J = 11.6 Hz, 1H), 4.12 (d, J = 14.8 Hz, 1H), 3.88 (t, J = 3.2 Hz, 1H), 3.79 (s, 3H), 3.67 (dd, J = 9.9, 3.3 Hz, 1H), 3.56 (dd, J = 9.9, 3.3 Hz, 1H), 2.83 (ddd, J =

12.7, 11.4, 3.8 Hz, 1H), 2.51−2.41 (m, 1H), 2.09 (dt, J = 17.4, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.2, 159.4, 153.6, 137.1, 129.7 (2C), 128.4 (2C), 128.1, 127.9, 127.8 (2C), 119.8, 114.2 (2C), 108.3, 73.6, 67.6, 58.5, 55.2, 48.4, 41.5, 22.9; HRMS (ESI-TOF): calcd for C$_{23}$H$_{26}$N$_3$O$_4$ [M + H]$^+$ 408.1923, found 408.1910.

(S)-3-(Hydroxymethyl)-2-(4-methoxybenzyl)-hexahydropyridazino[1,2-a][1,2,4]triazine-1,4-dione (5). To a solution of **4** (0.700 g, 1.72 mmol, 1 equiv) in EtOAc (50 mL) was added 20 wt % Pd(OH)$_2$ on carbon (140 mg) under argon. The resulting solution was stirred at room temperature under an atmosphere of hydrogen for 16 h. The reaction mixture was filtered over a pad of Celite, which was washed with EtOAc (2 × 50 mL). The filtrate was concentrated in vacuo and the resulting residue was purified by silica gel chromatography (gradient 50−100% of EtOAc in *n*-pentane) leading to **5** as a white amorphous solid (0.540 g, 1.69 mmol, 95%). R_f = 0.16 (EtOAc); $[\alpha]_D^{20}$ = +34.3 (*c* 0.15, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.20 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.91 (d, J = 14.8 Hz, 1H), 4.55 (brdd, J = 12.7, 3.5 Hz, 1H), 4.27 (brd, J = 12.0 Hz, 1H), 4.08 (d, J = 14.8 Hz, 1H), 3.79 (s, 3H), 3.78−3.71 (m, 3H), 2.99−2.85 (m, 3H), 1.82−1.74 (m, 3H), 1.61−1.48 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 162.6, 159.4, 156.2, 129.7 (2C), 127.8, 114.3 (2C), 59.7, 59.6, 55.3, 48.2, 48.1, 42.6, 23.6, 23.3; HRMS (ESI-TOF): calcd for C$_{16}$H$_{22}$N$_3$O$_4$ [M + H]$^+$ 320.1610, found 320.1608.

(S)-2-(4-Methoxybenzyl)-1,4-dioxooctahydropyridazino-[1,2-a][1,2,4]triazin-3-yl)methyl-4-methyl-benzenesulfonate (6). To a solution of **5** (1.34 g, 4.19 mmol, 1 equiv) in anhydrous DCM (80 mL) were added triethylamine (2.34 mL, 16.8 mmol, 4 equiv) and *p*-toluenesulfonyl chloride (3.20 mg, 16.8 mmol, 4 equiv) at 0 °C under argon. The reaction mixture was warmed to room temperature and stirred for 24 h. The resulting mixture was diluted with DCM (100 mL) and H$_2$O (100 mL) and the aqueous layer was extracted with DCM (3 × 120 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (gradient 0−50% of EtOAc in *n*-pentane) leading to **6** as a white amorphous solid (1.87 g, 3.94 mmol, 94%). R_f = 0.51 (EtOAc); $[\alpha]_D^{20}$ = +35.3 (*c* 0.36, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.76 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 4.76 (d, J = 14.8 Hz, 1H), 4.54 (dd, J = 12.7, 3.5 Hz, 1H), 4.36 (brd, J = 13.4 Hz, 1H), 4.11 (dd, J = 10.2, 2.3 Hz, 1H), 3.92 (dd, J = 10.2, 2.9 Hz, 1H), 3.85 (brt, J = 2.3 Hz, 1H), 3.78 (s, 3H), 3.77 (d, J = 14.8 Hz, 1H), 2.94 (td, J = 12.3, 2.6 Hz, 1H), 2.85 (td, J = 12.7, 2.4 Hz, 1H), 2.48 (s, 3H), 1.84−1.73 (m, 3H), 1.60−1.49 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.9, 159.6, 154.7, 145.5, 131.9, 130.0 (2C), 129.7 (2C), 128.3 (2C), 127.1, 114.5 (2C), 65.8, 57.0, 55.3, 48.1, 47.8, 42.9, 23.5, 23.2, 21.7; HRMS (ESI-TOF): calcd for C$_{23}$H$_{28}$N$_3$O$_6$S [M + H]$^+$ 474.1699, found 474.1698.

(S)-3-(Azidomethyl)-2-(4-methoxybenzyl)-hexahydropyridazino[1,2-a][1,2,4]triazine-1,4-dione (7). To a solution of **6** (1.075 g, 2.27 mmol, 1 equiv) in anhydrous DMF (30 mL) was added NaN$_3$ (0.267 g, 4.09 mmol, 1.8 equiv) at room temperature under argon. The reaction mixture was stirred at 40 °C for 6 h under argon, then quenched with saturated aqueous NaHCO$_3$ solution (5 mL), and concentrated in vacuo. The resulting residue was partitioned between EtOAc (75 mL) and H$_2$O (30 mL) and the aqueous layer was

extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (120 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (gradient 0−50% of EtOAc in *n*-pentane), leading to **7** as a white amorphous solid (0.727 g, 2.11 mmol, 93%). R_f = 0.24 (*n*-pentane/EtOAc, 1:1); $[\alpha]_D^{20}$ = +25.9 (*c* 0.21, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.24 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.70 (d, J = 14.8 Hz, 1H), 4.55 (brdd, J = 12.7, 3.7 Hz, 1H), 4.42 (brd, J = 12.6 Hz, 1H), 4.26 (d, J = 14.8 Hz, 1H), 3.85 (t, J = 3.1 Hz, 1H), 3.80 (s, 3H), 3.56 (dd, J = 12.8, 2.6 Hz, 1H), 3.34 (dd, J = 12.8, 3.8 Hz, 1H), 2.99 (td, J = 12.3, 2.8 Hz, 1H), 2.86 (td, J = 12.8, 2.7 Hz, 1H), 1.85−1.72 (m, 3H), 1.62−1.51 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 161.0, 159.6, 154.7, 129.8 (2C), 127.8, 114.4 (2C), 57.8, 55.3, 50.3, 48.8, 48.0, 42.8, 23.5, 23.2; HRMS (ESI-TOF): calcd for C$_{16}$H$_{21}$N$_6$O$_3$ [M + H]$^+$ 345.1675, found 345.1662.

(S)-3-(Azidomethyl)hexahydropyridazino[1,2-a][1,2,4]-triazine-1,4-dione (8). A solution of **7** (0.820 g, 2.38 mmol, 1 equiv) in a mixture TFA/H$_2$O/TIS (95:2.5:2.5, 8 mL) was stirred at 40 °C for 18 h and then concentrated in vacuo. The resulting residue was quenched with saturated aqueous NaHCO$_3$ solution until pH > 7 and diluted with EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (75 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (gradient 0−90% of EtOAc in *n*-pentane) leading to **8** as a white amorphous solid (0.419 g, 1.87 mmol, 79%). R_f = 0.15 (*n*-pentane/EtOAc, 1:4); $[\alpha]_D^{20}$ = −80.1 (*c* 0.14, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.44 (brs, 1H), 4.03−4.00 (m, 2H), 3.90−3.86 (m, 1H), 3.69 (d, J = 4.3 Hz, 2H), 3.48−3.43 (m, 2H), 1.79−1.65 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 161.5, 155.4, 53.8, 52.7, 46.3, 43.2, 23.3, 23.0; HRMS (ESI-TOF): calcd for C$_8$H$_{13}$N$_6$O$_2$ [M + H]$^+$ 225.1100, found 225.1094.

2-(4-Methoxybenzyl)-3-methylenehexahydropyridazino-[1,2-a][1,2,4]triazine-1,4-dione (9). To a solution of **5** (86 mg, 0.269 mmol, 1 equiv), 4-fluorophenol (31 mg, 0.269 mmol, 1 equiv), and triphenylphosphine (71 mg, 0.269 mmol, 1 equiv) in anhydrous THF (4 mL) was added diisopropyl azodicarboxylate (58 μL, 0.296 mmol, 1.1 equiv) at 0 °C under argon. The resulting mixture was stirred at room temperature for 6 h under argon. The mixture was concentrated in vacuo, partitioned between EtOAc (30 mL), and a saturated solution of NaHCO$_3$ (30 mL). The organic layer was separated and washed successively with H$_2$O (20 mL) and brine (20 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (gradient 0−40% of EtOAc in *n*-pentane), leading to **9** as a white amorphous solid (74 mg, 0.255 mmol, 91%). R_f = 0.31 (*n*-pentane/EtOAc, 1:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.18 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.48 (brd, J = 1.1 Hz, 1H), 4.85 (s, 2H), 4.68 (brd, J = 1.2 Hz, 1H), 3.88 (t, J = 5.7 Hz, 2H), 3.80 (t, J = 5.3 Hz, 2H), 3.78 (s, 3H), 1.88−1.83 (m, 2H), 1.79−1.75 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 158.9, 155.9, 151.2, 134.5, 128.1 (2C), 127.5, 114.1 (2C), 99.6, 55.2, 48.3, 47.7, 43.8, 23.4, 22.9; HRMS (ESI-TOF): calcd for C$_{16}$H$_{20}$N$_3$O$_3$ [M + H]$^+$ 302.1505, found 302.1503.

(S)-3-((4-Phenyl-1H-1,2,3-triazol-1-yl)methyl)-hexahydropyridazino[1,2-a][1,2,4]-triazine-1,4-dione (10a). Starting from **8** (18 mg, 0.080 mmol) and phenylacetylene (10

µL, 0.088 mmol), using general procedure A, **10a** was obtained as a white amorphous solid (25 mg, 0.077 mmol, 96%). R_f = 0.13 (DCM/MeOH, 9.8:0.2); $[\alpha]_D^{20}$ = −52.9 (c 0.11, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (s, 1H), 7.79 (d, J = 7.3 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 6.84 (brs, 1H), 4.90 (dd, J = 14.4, 3.8 Hz, 1H), 4.76 (dd, J = 14.4, 5.6 Hz, 1H), 4.45 (brt, J = 4.3 Hz, 1H), 3.73−3.64 (m, 2H), 3.49−3.46 (m, 1H), 3.33−3.30 (m, 1H), 1.68−1.59 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.2, 154.6, 148.0, 130.2, 128.9 (2C), 128.3, 125.7 (2C), 121.4, 54.1, 50.8, 45.0, 43.5, 23.1, 22.8; HRMS (ESI-TOF): calcd for C$_{16}$H$_{19}$N$_6$O$_2$ [M + H]$^+$ 327.1569, found 327.1561.

(S)-3-((4-(Thiophen-3-yl)-1H-1,2,3-triazol-1-yl)methyl)-hexahydropyridazino[1,2-a]-[1,2,4]triazine-1,4-dione (10b). Starting from **8** (20 mg, 0.089 mmol) and 3-ethynylthiophene (10 µL, 0.098 mmol), using general procedure A, **10b** was obtained as a white amorphous solid (28 mg, 0.084 mmol, 95%). R_f = 0.15 (EtOAc); $[\alpha]_D^{20}$ = −48.5 (c 0.10, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.86 (d, J = 2.5 Hz, 1H), 7.64 (dd, J = 4.8, 3.0 Hz, 1H), 7.56 (brd, J = 1.4 Hz, 1H), 7.51 (d, J = 5.0 Hz, 1H), 4.69 (dd, J = 14.3, 4.6 Hz, 1H), 4.60 (dd, J = 14.3, 4.8 Hz, 1H), 4.38−4.35 (m, 1H), 3.95 (dt, J = 12.6, 4.3 Hz, 1H), 3.61 (dt, J = 12.2, 4.2 Hz, 1H), 3.17 (ddd, J = 12.6, 10.1, 2.8 Hz, 1H), 2.76 (ddd, J = 12.4, 9.4, 3.1 Hz, 1H), 1.64−1.47 (m, 3H), 1.44−1.38 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 153.4, 142.8, 131.8, 127.1, 125.8, 122.2, 120.9, 53.8, 50.9, 44.8, 42.5, 22.9, 22.5; HRMS (ESI-TOF): calcd for C$_{14}$H$_{17}$N$_6$O$_2$S [M + H]$^+$ 333.1134, found 333.1117.

(S)-3-((4-(Pyridin-3-yl)-1H-1,2,3-triazol-1-yl)methyl)-hexahydropyridazino[1,2-a]-[1,2,4]triazine-1,4-dione (10c). Starting from **8** (20 mg, 0.089 mmol) and 3-ethynylpyridine (10 mg, 0.098 mmol), using general procedure A, **10c** was obtained as a white amorphous solid (22 mg, 0.067 mmol, 76%). R_f = 0.22 (DCM/MeOH, 9.6:0.4); $[\alpha]_D^{20}$ = −46.8 (c 0.10, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (d, J = 1.8 Hz, 1H), 8.60 (s, 1H), 8.55 (d, J = 4.8 Hz, 1H), 8.20 (d, J = 7.9 Hz, 1H), 7.57 (s, 1H), 7.49 (dd, J = 7.9, 4.8 Hz, 1H), 4.73 (dd, J = 14.3, 4.8 Hz, 1H), 4.65 (dd, J = 14.3, 4.6 Hz, 1H), 4.39 (brt, J = 4.5 Hz, 1H), 3.94 (dt, J = 12.6, 4.0 Hz, 1H), 3.62 (dt, J = 12.6, 4.5 Hz, 1H), 3.18 (ddd, J = 12.5, 10.1, 2.6 Hz, 1H), 2.77 (ddd, J = 12.4, 9.4, 3.1 Hz, 1H), 1.64−1.40 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.8, 153.4, 149.0, 146.4, 143.5, 132.5, 126.5, 124.0, 123.2, 53.8, 51.1, 44.7, 42.6, 22.9, 22.5; HRMS (ESI-TOF): calcd for C$_{15}$H$_{18}$N$_7$O$_2$ [M + H]$^+$ 328.1522, found 328.1508.

(S)-N-((1,4-Dioxooctahydropyridazino[1,2-a][1,2,4]-triazin-3-yl)methyl)benzamide (11a). Starting from **8** (0.100 g, 0.446 mmol) and benzoyl chloride (57 µL, 0.488 mmol), using general procedure B, **11a** was obtained as a white amorphous solid (0.125 g, 0.413 mmol, 93%). R_f = 0.13 (DCM/MeOH, 9.6:0.4); $[\alpha]_D^{20}$ = −32.7 (c 0.09, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.80 (d, J = 7.6 Hz, 2H), 7.50 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.19−7.17 (m, 1H), 6.41 (brs, 1H), 4.07−4.00 (m, 3H), 3.91 (brd, J = 12.4 Hz, 1H), 3.77−3.71 (m, 1H), 3.34−3.22 (m, 2H), 1.77−1.66 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.5, 163.7, 155.7, 133.7, 131.8, 128.5 (2C), 127.2 (2C), 54.0, 44.5, 43.4, 39.8, 23.4, 22.9; HRMS (ESI-TOF): calcd for C$_{15}$H$_{19}$N$_4$O$_3$ [M + H]$^+$ 303.1457, found 303.1457.

(S)-N-((1,4-Dioxooctahydropyridazino[1,2-a][1,2,4]-triazin-3-yl)methyl)-4-fluoro-benzamide (11b). Starting from **8** (20 mg, 0.089 mmol) and 4-fluorobenzoyl chloride (12 µL,

0,098 mmol), using general procedure B, **11b** was obtained as a white amorphous solid (22 mg, 0.069 mmol, 77%). R_f = 0.18 (DCM/MeOH, 9.6:0.4); $[\alpha]_D^{20}$ = −22.7 (c 0.18, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.83 (dd, J = 8.1, 5.6 Hz, 2H), 7.38 (brt, J = 5.9 Hz, 1H), 7.07 (t, J = 8.4 Hz, 2H), 6.75 (s, 1H), 4.06 (brt, J = 5.0 Hz, 1H), 4.01−3.93 (m, 2H), 3.78−3.67 (m, 2H), 3.44−3.32 (m, 2H), 1.75−1.65 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.4, 164.8 (d, $J_{C−F}$ = 252 Hz), 163.6, 155.8, 130.0 (d, $J_{C−F}$ = 3.0 Hz), 129.6 (d, $J_{C−F}$ = 9.0 Hz, 2C), 115.5 (d, $J_{C−F}$ = 21.9 Hz, 2C), 53.9, 44.7, 43.4, 40.3, 23.4, 22.9; ^{19}F NMR (376 MHz, CDCl$_3$) δ −107.7 (tt, J = 8.3, 5.6 Hz); HRMS (ESI-TOF): calcd for C$_{15}$H$_{18}$N$_4$O$_3$F [M + H]$^+$ 321.1363, found 321.1362.

(S)-N-((1,4-Dioxooctahydropyridazino[1,2-a][1,2,4]-triazin-3-yl)methyl)-3-methylbutan-amide (11c). Starting from **8** (30 mg, 0.134 mmol) and isovaleryl chloride (18 µL, 0,147 mmol), using general procedure B, **11c** was obtained as a white amorphous solid (32 mg, 0.114 mmol, 85%). R_f = 0.10 (DCM/MeOH, 9.6:0.4); $[\alpha]_D^{20}$ = −28.2 (c 0.12, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.30 (brt, J = 5.4 Hz, 1H), 5.96 (brs, 1H), 4.22−4.12 (m, 2H), 3.93 (t, J = 4.2 Hz, 1H), 3.91−3.84 (m, 1H), 3.52 (dt, J = 13.9, 4.7 Hz, 1H), 3.24−3.13 (m, 2H), 2.12−2.02 (m, 3H), 1.87−1.78 (m, 2H), 1.75−1.58 (m, 2H), 0.93 (d, J = 3.5 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 174.0, 163.9, 155.6, 53.9, 45.8, 44.5, 43.5, 38.6, 26.1, 23.4, 22.9, 22.4, 22.3; HRMS (ESI-TOF): calcd for C$_{13}$H$_{23}$N$_4$O$_3$ [M + H]$^+$ 283.1770, found 283.1775.

(2S,5S)-tert-Butyl-(1-(((1,4-dioxooctahydropyridazino[1,2-a][1,2,4]triazin-3-yl)methyl)-amino)-1-oxo-3-phenylpropan-2-yl)carbamate (11d). Starting from **8** (20 mg, 0.089 mmol) and Boc-L-phenylalanine (26 mg, 0.098 mmol), using general procedure C, **11d** was obtained as a white amorphous solid (33 mg, 0.074 mmol, 84%). R_f = 0.23 (DCM/MeOH, 9.6:0.4); $[\alpha]_D^{20}$ = −16.6 (c 0.13, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31−7.27 (m, 2H), 7.24−7.18 (m, 3H), 6.79 (brt, J = 5.7 Hz, 1H), 5.88 (brs, 1H), 5.31 (brd, J = 8.2 Hz, 1H), 4.35−4.33 (m, 1H), 4.01−3.98 (m, 2H), 3.80−3.72 (m, 2H), 3.49−3.41 (m, 1H), 3.36−3.26 (m, 2H), 3.08−2.98 (m, 2H), 1.79−1.62 (m, 4H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.7, 163.2, 155.4 (2C), 136.5, 129.3 (2C), 128.6 (2C), 126.9, 80.2, 56.0, 53.6, 44.7, 43.3, 39.3, 38.6, 28.3 (3C), 23.4, 22.9; HRMS (ESI-TOF): calcd for C$_{22}$H$_{32}$N$_5$O$_5$ [M + H]$^+$ 446.2403, found 446.2396. A small quantity of the other diastereomer (2R,5S) was detected by HPLC at 220 nm, t_R = 11.75 min (C18 Waters Sunfire column (1 mL min^{-1}, 215 nm, linear gradient 5−100% acetonitrile in water in 20 min, 0.1% TFA)), diastereomeric ratio (dr) (2S,5S)/(2R,5S): 94:6.

(2S,5R)-tert-Butyl-(1-(((1,4-dioxooctahydropyridazino[1,2-a][1,2,4]triazin-3-yl)methyl)-amino)-1-oxo-3-phenylpropan-2-yl)carbamate (11e). Starting from **8** (21 mg, 0.094 mmol) and Boc-D-phenylalanine (27 mg, 0.103 mmol), using general procedure C, **11e** was obtained as a white amorphous solid (40 mg, 0.090 mmol, 96%). R_f = 0.23 (DCM/MeOH, 9.6:0.4); $[\alpha]_D^{20}$ = −29.8 (c 0.10, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30−7.27 (m, 2H), 7.24−7.17 (m, 3H), 6.71 (brs, 1H), 5.98 (brs, 1H), 5.23 (brs, 1H), 4.35−4.34 (m, 1H), 4.06−4.02 (m, 2H), 3.80−3.72 (m, 2H), 3.42 (dt, J = 13.8, 5.8 Hz, 1H), 3.34−3.23 (m, 2H), 3.04 (brd, J = 4.9 Hz, 2H), 1.80−1.62 (m, 4H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.7, 163.4, 155.5 (2C), 136.5, 129.3 (2C), 128.6 (2C), 126.9, 80.2, 56.0, 53.4, 44.6, 43.3, 39.3, 38.6, 28.2 (3C), 23.4, 22.9; HRMS (ESI-TOF): calcd for C$_{22}$H$_{32}$N$_5$O$_5$ [M + H]$^+$ 446.2403, found 446.2392. A small quantity of the other diastereomer (2R,5R)

was detected by HPLC at 220 nm, t_R = 11.65 min (C18 Waters Sunfire column (1 mL min^{-1}, 215 nm, linear gradient 5−100% acetonitrile in water in 20 min, 0.1% TFA)), dr (2S,5R)/(2R,5R): 93:7.

tert-Butyl-(S)-((1,4-dioxooctahydropyridazino[1,2-a]-[1,2,4]triazin-3-yl)methyl)-carbamate (11f). To a solution of **8** (0.100 g, 0.446 mmol, 1 equiv) in dry MeOH (5 mL) was added 10 wt % Pd on carbon (10 mg) under argon. The resulting mixture was stirred at room temperature under a hydrogen atmosphere for 3 h. The reaction mixture was filtered over a pad of Celite, which was washed twiced with MeOH (2 × 10 mL). The filtrate was concentrated in vacuo and the resulting residue was straight away engaged in the next step. To a solution of the crude mixture in dry DCM (5 mL) was added Boc₂O (0.114 mL, 0.533 mmol, 1.2 equiv) at room temperature under argon. The reaction mixture was stirred at this temperature for 1 h under argon. The resulting mixture was diluted with DCM (20 mL) and H₂O (10 mL) and the aqueous layer was extracted three times with DCM (3 × 15 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (gradient 0−3% of MeOH in DCM) leading to **11f** as a white amorphous solid (0.125 g, 0.419 mmol, 94%). R_f = 0.16 (DCM/MeOH, 9.6:0.4); $[\alpha]_D^{20}$ = −55.1 (c 0.14, MeOH); ¹H NMR (400 MHz, DMSO-d_6) δ 7.18 (brs, 1H), 6.94 (brt, J = 6.0 Hz, 1H), 3.94−3.92 (m, 1H), 3.82−3.79 (m, 1H), 3.70 (td, J = 5.2, 2.1 Hz, 1H), 3.29−3.23 (m, 1H), 3.20−3.10 (m, 2H), 3.06 (dt, J = 13.9, 5.3 Hz, 1H), 1.68−1.50 (m, 4H), 1.37 (s, 9H); ¹³C NMR (100 MHz, DMSO-d_6) δ 162.3, 155.0, 153.9, 77.7, 53.4, 44.3, 42.0, 41.8, 27.7 (3C), 22.5, 21.9; HRMS (ESI-TOF): calcd for C₁₃H₂₃N₄O₄ [M + H]⁺ 299.1719, found 299.1713.

(S)-N-((1,4-Dioxo-2-(prop-2-yn-1-yl)octahydropyridazino-[1,2-a][1,2,4]triazin-3-yl)methyl)-benzamide (12a). Starting from **11a** (14 mg, 0.046 mmol) and propargyl bromide (80 wt % in toluene, 26 µL, 0.231 mmol), using general procedure D for 4 h, **12a** was obtained as a white amorphous solid (12 mg, 0.035 mmol, 75%). R_f = 0.23 (n-pentane/EtOAc, 3:7); $[\alpha]_D^{20}$ = +8.1 (c 0.14, MeOH); ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, J = 7.5 Hz, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 6.70 (brs, 1H), 4.39 (d, J = 17.8 Hz, 1H), 4.30−4.27 (m, 2H), 4.17 (d, J = 17.8 Hz, 1H), 4.07 (brd, J = 12.7 Hz, 1H), 4.00 (brdt, J = 14.0, 5.1 Hz, 1H), 3.84 (dt, J = 13.6, 6.5 Hz, 1H), 3.15−3.10 (m, 1H), 3.01 (ddd, J = 12.9, 10.2, 3.6 Hz, 1H), 2.37 (s, 1H), 1.80−1.64 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 167.6, 162.5, 153.8, 133.7, 131.8, 128.7 (2C), 127.0 (2C), 78.0, 73.8, 58.1, 46.2, 43.2, 39.0, 35.2, 23.5, 22.9; HRMS (ESI-TOF): calcd for C₁₈H₂₁N₄O₃ [M + H]⁺ 341.1614, found 341.1599.

(S)-N-((2-Butyl-1,4-dioxooctahydropyridazino[1,2-a]-[1,2,4]triazin-3-yl)methyl)-benzamide (12b). Starting from **11a** (19 mg, 0.063 mmol) and 1-bromobutane (34 µL, 0.314 mmol), using general procedure **D** for 24 h, **12b** was obtained as a white amorphous solid (14 mg, 0.039 mmol, 62%). Three equivalents of BEMP and 1-bromobutane were added after 6 h. R_f = 0.20 (n-pentane/EtOAc, 1:4); $[\alpha]_D^{20}$ = +8.6 (c 0.32, MeOH); ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, J = 7.5 Hz, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 6.67 (brs, 1H), 4.43 (brd, J = 12.9 Hz, 1H), 4.28 (brd, J = 12.3 Hz, 1H), 4.00 (dd, J = 8.4, 4.7 Hz, 1H), 3.91−3.78 (m, 2H), 3.52 (ddd, J = 13.7, 8.3, 5.7, 1H), 3.01−2.89 (m, 3H), 1.84−1.67 (m, 3H), 1.62−1.56 (m, 3H), 1.32 (sxt, J = 7.1 Hz, 2H), 0.92

(t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.6, 162.8, 154.1, 133.7, 131.8, 128.6 (2C), 127.0 (2C), 58.6, 46.0, 45.9, 43.1, 40.1, 30.1, 23.6, 23.0, 19.9, 13.7; HRMS (ESI-TOF): calcd for C₁₉H₂₇N₄O₃ [M + H]⁺ 359.2083, found 359.2064.

tert-Butyl-(S)-(3-(3-(benzamidomethyl)-1,4-dioxohexahydropyridazino[1,2-a][1,2,4]-triazin-2(1H)-yl)-propyl)carbamate (12c). Starting from **11a** (20 mg, 0.066 mmol) and 3-(Boc-amino)propyl bromide (79 mg, 0.331 mmol), using general procedure D for 24 h, **12c** was obtained as a white amorphous solid (19 mg, 0.041 mmol, 60%). Three equivalents of BEMP and 3-(Boc-amino)propyl bromide were added after 6 h. R_f = 0.12 (pentane/EtOAc, 1:4); $[\alpha]_D^{20}$ = +15.4 (c 0.17, MeOH); ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, J = 7.6 Hz, 2H), 7.52 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 6.77 (brs, 1H), 5.08 (brs, 1H), 4.41 (brd, J = 12.6 Hz, 1H), 4.22 (brd, J = 12.8 Hz, 1H), 4.00 (dd, J = 8.0, 4.4 Hz, 1H), 3.89 (dt, J = 13.4, 5.4 Hz, 1H), 3.79−3.72 (m, 1H), 3.60−3.53 (m, 1H), 3.25−3.06 (m, 3H), 3.01−2.89 (m, 2H), 1.84−1.71 (m, 5H), 1.63−1.57 (m, 1H), 1.44 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 167.8, 162.6, 156.1, 154.4, 133.7, 131.8, 128.6 (2C), 127.0 (2C), 79.1, 59.3, 45.9, 43.8, 43.1, 40.3, 37.5, 28.7, 28.4 (3C), 23.5, 22.9; HRMS (ESI-TOF): calcd for C₂₃H₃₄N₅O₅ [M + H]⁺ 460.2560, found 460.2543.

(S)-N-((2-Isobutyl-1,4-dioxooctahydropyridazino[1,2-a]-[1,2,4]triazin-3-yl)methyl)-benzamide (12d). Starting from **11a** (30 mg, 0.099 mmol) and 1-bromo-2-methylpropane (54 µL, 0.496 mmol), using general procedure D for 48 h, **12d** was obtained as a white amorphous solid (4 mg, 0.039 mmol, 11%). Three equivalents of BEMP and 1-bromo-2-methyl-propane were added after 6 h. R_f = 0.23 (EtOAc); $[\alpha]_D^{20}$ = +7.7 (c 0.20, MeOH); ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, J = 7.3 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 6.58 (brs, 1H), 4.50 (brd, J = 12.7 Hz, 1H), 4.35 (br d, J = 12.6 Hz, 1H), 3.99 (dd, J = 8.5, 4.9 Hz, 1H), 3.89−3.83 (m, 1H), 3.77 (dd, J = 13.8, 8.0 Hz, 1H), 3.52 (ddd, J = 13.6, 8.4, 5.6 Hz, 1H), 2.95−2.85 (m, 2H), 2.69 (dd, J = 13.9, 7.0 Hz, 1H), 1.91 (sept, J = 6.8 Hz, 1H), 1.88−1.72 (m, 3H), 1.61−1.53 (m, 1H), 0.92 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.7, 162.8, 154.3, 133.7, 131.9, 128.7 (2C), 127.0 (2C), 59.4, 53.3, 46.0, 43.1, 40.1, 27.3, 23.6, 23.0, 20.0, 19.7; HRMS (ESI-TOF): calcd for C₁₉H₂₇N₄O₃ [M + H]⁺ 359.2083, found 359.2080.

(S)-N-((2-(4-Fluorobenzyl)-1,4-dioxooctahydropyridazino-[1,2-a][1,2,4]triazin-3-yl)methyl)-benzamide (12e). Starting from **11a** (30 mg, 0.099 mmol) and 4-fluorobenzyl bromide (62 µL, 0.496 mmol), using general procedure D for 3 h, **12e** was obtained as a white amorphous solid (32 mg, 0.078 mmol, 79%). R_f = 0.24 (n-pentane/EtOAc, 1:4); $[\alpha]_D^{20}$ = +39.9 (c 0.27, MeOH); ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, J = 7.7 Hz, 2H), 7.50 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 7.30 (dd, J = 7.3, 5.8 Hz, 2H), 7.01 (t, J = 8.5 Hz, 2H), 6.65 (brt, J = 4.8 Hz, 1H), 4.92 (d, J = 15.1 Hz, 1H), 4.41 (brd, J = 12.8 Hz, 1H), 4.28 (brd, J = 11.7 Hz, 1H), 4.24 (d, J = 15.1 Hz, 1H), 3.92 (dd, J = 7.7, 4.5 Hz, 1H), 3.70 (ddd, J = 13.8, 5.4, 4.9 Hz, 1H), 3.58 (ddd, J = 13.8, 7.4, 6.4 Hz, 1H), 2.98−2.91 (m, 2H), 1.83−1.66 (m, 3H), 1.61−1.51 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 167.7, 162.5 (d, J_{C-F} = 247 Hz), 162.4, 154.2, 133.6, 132.0 (d, J_{C-F} = 3.2 Hz), 131.8, 130.1 (d, J_{C-F} = 8.1 Hz, 2C), 128.6 (2C), 127.0 (2C), 115.8 (d, J_{C-F} = 21.5 Hz, 2C), 58.0, 48.5, 46.3, 43.1, 39.5, 23.5, 22.9; ¹⁹F NMR (376 MHz, CDCl₃) δ −113.9 to −114.0 (m); HRMS (ESI-TOF): calcd for C₂₂H₂₄N₄O₃F [M + H]⁺ 411.1832, found 411.1826.

■ ASSOCIATED CONTENT

ⓈSupporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b01752.

¹H NMR and ¹³C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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